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THEORY AND METHODS

Overestimation of complication rates in evaluations of *Chlamydia trachomatis* screening programmes—implications for cost-effectiveness analyses

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Background Cost-effectiveness analyses of screening programmes for asymptomatic *Chlamydia trachomatis* infection suggest that screening at low prevalences in the population is cost-effective. However, the decision models in these studies are based on assumptions about the risk of complications, which are derived from the literature. Incorrect assumptions may lead to under- or overestimation of the effectiveness of screening. The first objective of this paper is to evaluate the assumptions about the probability of complications after an asymptomatic *C. trachomatis* infection. The second objective is to calculate alternative rates by using available data on the incidence of complications.

Methods We identified cost-effectiveness studies via Medline, and evaluated these for the evidence for the quoted probabilities. In addition, the probability of complications was calculated for Amsterdam from available registration data.

Results In the three studies that were identified, the assumptions for the rates of pelvic inflammatory disease (PID) (clinical and subclinical) after *C. trachomatis* infection varied from 15% to 80%, and for ectopic pregnancy, tubal factor infertility, and chronic pelvic pain after PID from 5–25%, 10–20%, and 18–30%, respectively. The assumptions were based on data from high-risk populations, case-control data, and data not accounting for misdiagnoses. Using data obtained from local registrations, we estimated the probability of a clinical PID (0.43%), ectopic pregnancy (0.07%), and tubal factor infertility (0.02%) for women with a current infection. These estimates were consistently lower than the estimates based on the literature.

Conclusions We argue that an overestimation of the current complication rates is likely. The effect of overestimation is potentially the greatest in populations with a low prevalence, since the currently assumed cost savings associated with screening may disappear when using more realistic estimates for complications.

Keywords Mass screening, *Chlamydia trachomatis*, salpingitis, pelvic inflammatory disease, infertility, costs and cost analysis, ectopic pregnancy

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A genital *Chlamydia trachomatis* infection is the most prevalent bacterial sexually transmitted infection in The Netherlands, as well as in other industrialized countries.[1] Chlamydial infections are often asymptomatic and may therefore remain untreated. In women, an untreated infection can lead to pelvic inflammatory disease (PID), chronic pelvic pain, and, at a later stage, to ectopic pregnancy and tubal factor infertility.[2,3] The introduction of sensitive non-invasive tests and single-dose treatment regimens has opened the way to large-scale screening for asymptomatic disease.[4–7] Active detection of chlamydial infections, in order to prevent these complications, has therefore become an important public health issue.[8,9] Screening a population at high risk for asymptomatic infections has been shown to reduce the incidence of PID by more than half.[3] Furthermore, cost-effectiveness analyses of studies performed in different settings suggest that screening becomes cost-effective at prevalences of 2–10%.[10–13]

These analyses are based on decision models that include assumptions about the risk of complications, which are derived from the medical literature. These risks are often estimated on the basis of populations that are at higher risk of developing complications, or on the basis of data derived from case-control studies. The problem with this approach is that the risk can easily be wrongly estimated, which could lead to under- or over-estimation of the (cost-) effectiveness of screening. Sensitivity analyses can be performed to explore the potential impact of this uncertainty. However, these analyses may not be valid if the range across which the incidences are varied is incorrect and does not contain the true population value.

A flawed cost-effectiveness analysis (CEA) may have great implications for health care policy, resulting in an unjustifiable implementation of expensive health prevention programmes. Hence, the purpose of this study is, firstly, to assess the validity of current assumptions about the probability of developing PID, tubal factor infertility, ectopic pregnancy, and chronic pelvic pain after an asymptomatic chlamydial infection. Secondly, to calculate alternative rates of complications after asymptomatic *C. trachomatis* infection by using available data from national and local registrations.

Methods

Literature

A computerized Medline search was carried out to identify articles published in the international medical literature (English) between January 1994 and September 2000. Terms used for the search were 'cost-effectiveness analysis' or 'decision analysis' or 'cost', and '*Chlamydia trachomatis*'. To be included in the analysis, the CEA had to report on: (1) a screening programme aimed at females, (2) a decision model for asymptomatic *C. trachomatis* infections, and (3) the estimated values (and references) for risk of complications after an asymptomatic infection.

Complications considered in this evaluation were: sub-clinical PID, clinical PID, tubal factor infertility, ectopic pregnancy, and chronic pelvic pain. From the CEA we identified the point estimates for the risk of these complications and, if stated, the range considered for a sensitivity analysis. The corresponding references were traced, and evaluated by three of the authors (IGMvV, SAM, and AJPB) on the design, the interpretation of the results, and suitability of the source data for estimation of the risk of complications in the CEA. The aspect of suitability implies that whilst the study in itself may be valid, it may be completely unsuitable for the quantification of the risk of complications after an asymptomatic infection.

Several examples of the problems and inappropriateness of the source data will be discussed in Results. For reasons of brevity, not all information from the studies will be discussed.

Alternative calculation of complication rates

We calculated the probability of complications of *C. trachomatis* based on available registration data and data from several (local) studies. The prevalence of *C. trachomatis* infections among women in Amsterdam was derived from a study performed by Van Valkengoed *et al*.[14] Data on the incidence of clinical PID were obtained from general practice registers.[15] Data on the occurrence of tubal factor infertility were obtained from Van de Lisdonk *et al*.[16] Data on the occurrence of ectopic pregnancies were derived from the National Morbitity and Mortality Registers.[17] The population demographics for Amsterdam were derived from the official Municipal Population Register.[18]

Several corrections were made, based on the literature, to take into account factors such as the number of clinical misdiagnoses and non-chlamydia-related episodes of disease.

Finally, the calculated rates for Amsterdam were compared with the estimated rates, based on the assumptions from the literature. Furthermore, several of the assumed incidences of complications in the CEA were compared with reported incidences of complications in the countries where the CEA were performed.

Results

Literature

We identified five CEA of screening programmes that met the inclusion criteria. However, only three reported the probabilities included in the decision models.[10,11,19] Two CEA concerned screening programmes in the US among asymptomatic women attending a family planning clinic or a sexually transmitted disease (STD) clinic,[10,19] and one concerned a screening programme in Finland among asymptomatic women attending a gynaecology and obstetrics clinic.[11]

Table 1 shows the assumptions for the risk of various complications after asymptomatic *C. trachomatis* infection included in the decision models for these CEA. The estimate for the total incidence of PID after an asymptomatic *C. trachomatis* infection varies from 25% to 80%, including an estimated 10–20% probability of clinical or overt PID.[3,10,20–30] One study reports a sensitivity analysis with a range of 15–40% for all PID.[10] The estimated risk of a clinical and sub-clinical PID leading to ectopic pregnancy varies between 5 and 25%.[2,21,31–34] A tubal factor infertility is assumed to occur among 10–20% of all women with a chlamydia-related PID,[2,31,35–41] and chronic pelvic pain among 18–30%.

Table 1 Evidence for the estimated probabilities of developing complications after *Chlamydia trachomatis* (CT) infection, used in cost effectiveness analysis (CEA) models for CT screening programmes

CEA	Estimated probability of events[a]	Predicted CT-related incidence/ 10 000 women	Target population CEA	References	Problems or inappropriateness of source data
Marrazzo *et al.*, 1997	PID[b]	165	Asymptomatic women attending a family planning clinic or an STD[d] clinic, 6.6% prevalence CT	Cates, 1991	Review
	All: 25%[c]			Cates, 1993	No diagnostic confirmation 'asymptomatic' PID
	Clinical: 10%			Cumming, 1988[e]	Diagnosis of PID at time of surgery for EP[f], women at high risk
	Sub-clinical: 15%			Paavonen, 1985	Women at higher risk, diagnosis CT by serology, women had several co-infections
				Stamm, 1984	PID diagnosis unconfirmed, gonorrhoea is possible cause for PID, women at high risk
				Stamm, 1990	Review
	EP	8.3		Cates, 1991	Review
	All: 5%[g]			Weström, 1981	Symptomatic women, misclassification
	TFI[h]	16.5		Brunham, 1985	Clinical diagnosis of TFI, serologic diagnosis of CT (causal role), case-control data
	All: 10%[i]			Cates, 1990	Review
				Sellors, 1988	Case-control study, CT diagnosis by detection of serological antibodies
				Svensson, 1983	Women infected with gonorrhoea
				Weström, 1992	Symptomatic cases
	CPP[j]	29.7		Weström, 1980	Symptomatic women, possible biased diagnosis of CPP
	All: 18%				
Paavonen *et al.*, 1998	PID[b]	400	Asymptomatic women attending a gynaecology and obstetrics clinic, 5% prevalence CT	Brunham, 1987	Women at higher risk (invasive procedure)
	All: 80%			Cates, 1993	No diagnostic confirmation 'asymptomatic' PID
	Clinical: 20%			Paavonen, 1985	Women at higher risk, diagnosis CT by serology, women had several co-infections
	Sub-clinical: 60%			Platt, 1983	No CT diagnosis, unconfirmed PID
				Stamm, 1984	PID diagnosis unconfirmed, Gonorrhoea is possible cause for PID, women at high risk
				Wölner-Hansen, 1990	Review
	EP	100		Makinen, 1997	Calculation error
	All: 25%			Weström, 1981	Symptomatic women, misclassification
	TFI	80		McCormack, 1994	Review
	All: 20%			Weström, 1980	Review
				Weström, 1994	Symptomatic cases
	CPP	120			
	All: 30%				

Howell *et al.*, 1998	PID All: 30% Clinical: 12% Sub-clinical: 18%	198	Asymptomatic women attending an family planning clinic, 6.6% prevalence CT	Jones, 1986 Marrazzo, 1997 Rees, 1980 Scholes, 1996 Stamm,1984	Women at high risk, no PID diagnosis CEA Women with gonorrhoea, no chlamydia High risk population, unconfirmed PID PID diagnosis unconfirmed, gonorrhoea is possible cause for PID, women at high risk
	EP All: 7.8%	15.5		Haddix, 1995 Washington, 1991 Weström, 1992	CEA No follow-up data Symptomatic women
	TFI All: 12%	23.8		Haddix, 1995 Weström,1992	CEA Symptomatic cases
	CPP All: 18.1%	35.9		Haddix, 1995 Washington, 1991	CEA No follow-up data

[a] Estimated probabilities of sub-clinical and clinical pelvic inflammatory disease after (a) symptomatic *CT* infection and ectopic pregnancy/tubal factor infertility/chronic pelvic pain after a pelvic inflammatory disease.

[b] Pelvic inflammatory disease.

[c] A range of 15–40% for all pelvic inflammatory disease considered in sensitivity analysis.

[d] Sexually transmitted disease.

[e] Author listed as Cumining in reference list.

[f] Ectopic pregnancy.

[g] A range of 5–10% for EP reportedly considered in sensitivity analysis, results not reported.

[h] Tubal factor infertility.

[i] A range of 10–20% for TFI is reportedly considered in the sensitivity analysis, results not reported.

[j] Chronic pelvic pain.

The evidence

Evidence for the estimates for the occurrence of these complications is derived from various studies. Several validity issues are involved:

The population is at greater risk of infection or at greater risk of developing complications than the population for which the programme is designed

In one study, women were selected on the basis of a high-risk profile for STD.[3] The circulation of *C. trachomatis* infections in this population is probably higher, and they may have already had multiple infections, which implies that they have a greater cumulative chance of developing or having developed complications.[42] Moreover, among women who are at high risk of developing a *C. trachomatis* infection, the prevalence of other sexually transmitted pathogens, that may also cause PID, will most likely also be high.[43] In two other studies, the occurrence of PID among women with clear symptoms of infection (mucopurulent cervicitis) and women undergoing an abortion was studied.[20,25] It has been well documented that the risk of PID increases after this type of invasive procedure.[44,45]

Assumptions are made solely based on case-control data

Several estimates, such as the probability of clinical PID, were based on case-control studies.[21] The odds ratios were misinterpreted as relative risks, which may lead to over-estimation of the actual risk. In addition, the absolute risk of developing PID after a chlamydial infection cannot be derived from a case-control study.

Diagnosis by exclusion, gaps in the knowledge, and unsubstantiated assumptions

An example of a gap in the knowledge about *C. trachomatis* is the concept of sub-clinical PID, which has been postulated to explain the pathway of cervical chlamydial infection to infertility or ectopic pregnancy, without there being obvious signs of an infection.[46] Sub-clinical PID is mostly diagnosed retrospectively by exclusion of other possible causes for the complications; i.e. if there is no evidence of a prior clinical PID, the PID must have been sub-clinical. For example, in one study, tubal damage observed among women consulting for (tubal factor) infertility, who had never had a (self-reported) PID, was attributed to a previous sub-clinical PID.[22] However, women may not have had a PID or women may just not remember having experienced a PID.

Moreover, in all the CEA the risk of ectopic pregnancy, tubal factor infertility, and chronic pelvic pain after sub-clinical PID is assumed to be equal to the risk after clinical PID. However, Weström *et al*. have shown that the risk of developing complications varies considerably, depending on the severity of the PID.[2] Based on data from their prospective studies, it seems fair to assume that sub-clinical or mild PID are most likely to result in lower probabilities of ectopic pregnancy than symptomatic or severe PID.[2]

Another issue that needs more attention is chronic pelvic pain. Only one prospective study is quoted in two CEA to support the 18% probability of chronic pelvic pain.[41] (Table 1) This study refers to Weström *et al*.,[47] who reported that 18.1% of women with PID reported that they suffered from chronic pelvic pain. No further (prospective) studies have been performed to confirm these results.

Misclassification and incorrect diagnoses

C. trachomatis infections, as well as complications, are not or incorrectly diagnosed in some studies. In one study, the PID rate among women infected with gonorrhoea was studied, and the presence of *C. trachomatis* was not established at all.[26] Moreover, complications were often self-reported or clinically diagnosed and not confirmed by appropriate diagnostic methods; e.g. the clinical diagnosis of PID, which cannot be confirmed in approximately 30% of the cases.[48,49] Lastly, misclassification is also apparent in a study that increases the probability of ectopic pregnancy after PID by including in the PID group women with ectopic pregnancy, for whom the damage to the tubes was only discovered at the time of surgery for ectopic pregnancy.[34] This implies the assumption that all women with PID will develop ectopic pregnancy. However, the women in the non-ectopic pregnancy group could also be suffering from undiagnosed PID.

Calculations of the complication rates

An illustrative example of calculation error is the analysis of Finnish national data by Paavonen *et al*.[11] Despite the fact that their population does not consist of pregnant women, the authors use the incidence of ectopic pregnancy per 1000 pregnancies, instead of the lower figure that is given for all women.[32] In addition, applying a tenfold increase in the number of ectopic pregnancies to account for the increase in risk after PID does not take into account the fact that the reported incidence of ectopic pregnancy already includes all PID-related ectopic pregnancies. This again considerably overestimates the probability of ectopic pregnancy after PID.

Alternative calculation of complication rates

Figure 1 shows the alternative calculation of the probability of complications after *C. trachomatis* infection, based on available registration data and the prevalence found in Amsterdam, The Netherlands. In 1997, the prevalence of *C. trachomatis* infections among women in Amsterdam was found to be 2.9%.[14] The prevalence was determined in a study based on home-obtained urine samples from 5714 women randomly selected from general practice computer registers. According to the Municipal Population Register, approximately 151 087 women in the age category 15–40 years lived in Amsterdam,[18] and with an estimated prevalence of 3% it can be calculated that 4556 of these women have a *C. trachomatis* infection.

Clinical PID

In Amsterdam, the annual incidence of clinically diagnosed PID in 1990 was 48.5 per 10 000 woman-years for women aged 15–44 years. More recent data are not available. However, national surveillance data show a stable incidence in urbanized areas over the years 1993–1997.[15]

Only 70% of clinically diagnosed PID can be confirmed laparoscopically,[48,49] resulting in a true incidence of 34 PID per 10 000 women. It is difficult to determine which percentage of PID is causally related to chlamydial infection. Serological evidence of *C. trachomatis* infection is found in approximately 50% of women with PID.[21] Not taking into account possible false-positive or false-negative results, it can be assumed that among women with no serological evidence of infection, the occurrence of a chlamydia-related PID is very unlikely. Thus, 50% of PID is the maximum number that could

A.

$$\textbf{Pr\{clinical PID | chlamydia\}} = \frac{\textbf{Pr\{chlamydia | clinical PID\}} * \textbf{Pr\{clinical PID\}}}{\textbf{Pr\{chlamydia\}}}$$

Pr{chlamydia}= 0.03

Pr{clinical PID} = Pr{clinical PID | clinically diagnosed PID}* Pr{clinically diagnosed PID}=0.70*0.00485

$$\text{Pr\{chlamydia | clinical PID\}} = \text{Pr\{chlamydia serology | clinical PID\}} * \frac{\text{Pr\{chlamydia\}}* \text{Pr\{chlamydia serology | chlamydia\}}}{\text{Pr\{no chlamydia\}}* \text{Pr\{chlamydia serology | no chlamydia\}}+\text{Pr\{chlamydia\}}* \text{Pr\{chlamydia serology | chlamydia\}}}$$

= 0.50* 0.03*0.70 / (0.97*0.26 + 0.03*0.70)

(references: 14,15,21,48,49,50,personal communication SAM)

B.

$$\textbf{Pr\{EP | chlamydia\}} = \frac{\textbf{Pr\{chlamydia | EP\}} * \textbf{Pr\{EP\}}}{\textbf{Pr\{chlamydia\}}}$$

Pr{chlamydia}= 0.03

Pr{EP} =0.0007

$$\text{Pr\{chlamydia | EP\}} = \text{Pr\{chlamydia serology | EP\}} * \frac{\text{Pr\{chlamydia\}}* \text{Pr\{chlamydia serology | chlamydia\}}}{\text{Pr\{no chlamydia\}}* \text{Pr\{chlamydia serology | no chlamydia\}}+\text{Pr\{chlamydia\}}* \text{Pr\{chlamydia serology | chlamydia\}}}$$

= 0.40* 0.03*0.70 / (0.97*0.26 + 0.03*0.70)

(references: 14,16,17,50,51,personal communication SAM)

C.

$$\textbf{Pr\{TFI | chlamydia\}} = \frac{\textbf{Pr\{chlamydia | TFI\}} * \textbf{Pr\{TFI\}}}{\textbf{Pr\{chlamydia\}}}$$

Pr{chlamydia} = 0.03

Pr{TFI} = Pr{TFI | Subfertility}* Pr{Subfertility} =0.14*0.0020

$$\text{Pr\{chlamydia | TFI\}} = \text{Pr\{chlamydia serology | TFI\}} * \frac{\text{Pr\{chlamydia\}}* \text{Pr\{chlamydia serology | chlamydia\}}}{\text{Pr\{no chlamydia\}}* \text{Pr\{chlamydia serology | no chlamydia\}}+\text{Pr\{chlamydia\}}* \text{Pr\{chlamydia serology | chlamydia\}}}$$

= 0.30* 0.03*0.70 / (0.97*0.26 + 0.03*0.70)

(references: 14,16,50,53,54,personal communication SAM)

Figure 1 Calculation of the probability of pelvic inflammatory disease (a), ectopic pregnancy (b), and tubal factor infertility (c)

have been caused by *C. trachomatis*, resulting in an incidence of 17 PID per 10 000 women, although it must be said that it is very unlikely that *C. trachomatis* is actually the (only) causal agent in all cases. Every year, a total of 257 of clinical PID with evidence of past *C. trachomatis* infection will occur in Amsterdam.

One way of taking into account that women without a current infection may have had an infection in the past, is to look at the seroprevalence of chlamydia in women with a current *C. trachomatis* infection and women without a current infection. In a recent Dutch study, serological evidence of *C. trachomatis* was found among 70% of women who tested positive for genital *C. trachomatis* infection by means of polymerase chain reaction (PCR) and 26% of women who tested negative. (personal communication, SAM) Similar results were reported in a study among Danish women.[50] In Amsterdam, 3189 of the 4556 (70%) women with a genital *C. trachomatis* infection and 38 098 of the 146 531 (26%) women without a genital *C. trachomatis* infection are seropositive. Among the total number of 41 287 (3189 + 38 098) women with serological evidence of infection 257 clinical PID will occur per year: 237 among women without a current *C. trachomatis* infection, but with serological evidence of infection, and 20 among women with a current *C. trachomatis* infection and serological evidence of infection. The rate among 4556 women with a current genital infection, of whom 3189 are seropositive at diagnosis, is 0.43%.

Ectopic pregnancy

For ectopic pregnancy, similar calculations can be made. However, no regional registration data for Amsterdam are available. Nationwide surveillance systems report an annual incidence of 2000 ectopic pregnancies,[15,17] some of which occur among women under 15 or over 40 years of age.

Table 2 The estimated probability of complications, calculated on the basis of current assumptions and actual probabilities, based on observed occurrence of complications in Amsterdam

	Estimated based on current assumptions		Estimated based on registration data	
	Probability (%)*	Cases due to current CT*	Probability (%)	Cases due to current CT*
Clinical PID	6–20	274–912	0.43	21
Ectopic pregnancy#	0.75–20	35–912	0.07**	4
Tubal factor infertility#	1.5–16	69–729	0.02***	1

PID = pelvic inflammatory disease, CT = *Chlamydia trachomatis.*

After clinical and sub-clinical PID.

* These ranges were calculated with the minimum and maximum rates presented in the CEAs, including reported sensitivity analysis minimum and maximum values. Ranges for: all PID 15–80% (9–60% is sub-clinical), ectopic pregnancy 5–25% after PID and tubal factor infertility 10–20% after PID (see Table 1).

** For ectopic pregnancy, national registration data were used instead of data from Amsterdam general practice registers.

*** The probability would be 0.009%, if taking into account the fact that approximately 60% of couples are not infertile, which is apparent from the fact that they conceive while on a waiting list for treatment.[55]

Approximately 2 980 430 women in the age category of 15–40 years live in The Netherlands.[17] Assuming that all reported ectopic pregnancies occur in this age category, it can be deduced that the annual incidence is 7 per 10 000 woman-years. However, some of these ectopic pregnancies are not chlamydia-related. In a previous Dutch study, evidence of prior chlamydial infection was found in 40% of women with an ectopic pregnancy.[51] The maximum probability of chlamydia-related ectopic pregnancies is therefore 3 per 10 000 woman-years. This implies that 42 potentially chlamydiarelated ectopic pregnancies occur in Amsterdam each year, of which 3.2 occur among women with a current infection and serological evidence of *C. trachomatis*. The rate of ectopic pregnancy among the women with a current genital infection is 0.07%.

This is the maximum probability of ectopic pregnancy after *C. trachomatis* infection, as there are many other causes of ectopic pregnancy which have not been taken into account. Finally, probabilities for the entire female population should be inflated slightly to take into account women who have damaged tubes, but are not currently seeking pregnancy.

Tubal factor infertility

The estimated incidence of sub-fertility for Amsterdam is 20 per 10 000 woman-years.[16] It is estimated that 14–16.5% of these couples seek specialist medical care for their fertility problem.[52] Previous research has also shown that approximately 14% of infertility is due to a tubal factor:[53] an incidence of 2.8 per 10 000 woman-years for Amsterdam. No serological evidence of chlamydia infection was found in a total of 73% of women suffering from tubal factor infertility.[54] It is therefore assumed that a maximum of 30% of all tubal factor infertilities are attributable to *C. trachomatis*, resulting in an annual incidence of 0.84 per 10 000 women.

Among the 4556 women with *C. trachomatis* in Amsterdam, of whom 3189 (70%) have serological evidence of the infection, 0.98 cases of tubal factor infertility will eventually occur. The maximum probability of tubal factor infertility after chlamydial infection will then be 0.02%.

If we take into account the fact that approximately 60% of couples conceive while on a waiting list for treatment,[55] thus indicating that they are not infertile, the probability of tubal factor infertility after chlamydial infection would be 0.009%.

Finally, these probabilities should be inflated to compensate for the number of women who have become infertile due to *C. trachomatis*, but are not currently seeking pregnancy.

Chronic pelvic pain

Data on chronic pelvic pain diagnoses are not available from any source.

Calculated versus estimated probabilities

Table 2 shows the calculated probabilities of clinical PID, ectopic pregnancy, and tubal factor infertility, based on current assumptions used in the three CEA, and the probabilities calculated on the basis of the observed occurrence of complications in Amsterdam. For all complications of *C. trachomatis*, the modelled probability is higher than the probabilities calculated on the basis of registration data from Amsterdam.

We also compared several estimated rates from the CEA studies (Table 1) to available data from local registrations reported in the literature. Firstly, the ectopic pregnancy rates for Finland. The incidence of ectopic pregnancies (all causes) in Finland is 15.3 per 10 000 fertile-aged women,[32] whereas the estimated incidence among Finnish women due to *C. trachomatis*, using the assumptions from the CEA by Paavonen *et al.*, was 100 ectopic pregnancies per 10 000.[11]

Secondly, the rate of PID in the western part and southern part of the US. In the CEA by Marrazzo *et al.* (Western US) and Howell *et al.* (Southern US), it is estimated that the incidence of clinical PID due to *C. trachomatis* is 66 and 79.2 per 10 000 women, respectively.[10,19] Rates from a study performed with data from the 1989–1990 Hospital Discharge Surveys indicate that in the Western US, the PID rate per 10 000 women of reproductive age, caused by any agent and not discounted for potential clinical misdiagnoses, is 34.1. In the Southern US the total annual incidence is 62.3 per 10 000.[56]

Lastly, we looked at the estimated rate of ectopic pregnancy in the CEA from the US. The estimated incidence of ectopic pregnancy due to a single episode of *C. trachomatis* in the CEA was 8.3 (Western) and 15.5 (Southern) per 10 000 women (Table 1). In 1992, the reported cases of ectopic pregnancies in the US accounted for approximately 2% of the total number of pregnancies, a rate of 19.7 per 1000 pregnancies.[57] The reported pregnancy rate per 1000 women in that year was 111.8.[58] Thus, the total incidence of ectopic pregnancy is 22.4

per 10 000 women. Although the estimated incidences due to *C. trachomatis* are lower than the observed total incidence, it is not immediately clear whether the estimated rates are reasonable, as it is unclear how many of the reported ectopic pregnancies are chlamydia-related. Unfortunately, the strategy presented above to determine the rates in Amsterdam could not be applied, as local data on *C. trachomatis* antibodies among women with ectopic pregnancy and among women from the general population were not available.

Discussion

Literature

Three studies on the cost-effectiveness of screening women for asymptomatic *C. trachomatis* infections were reviewed.[10,11,19] Estimates for all PID, tubal factor infertility, and ectopic pregnancy varied from 25–80%, 10–20%, and 5–25%, respectively. (Table 1) Only one study reported the performance of a sensitivity analysis for the probabilities of developing complications.[10] However, only the sensitivity analysis for PID was reported (range 15–40%). When reviewing the supporting evidence, the general trend was towards a considerable overestimation of the risk of complications after an asymptomatic *C. trachomatis* infection.

The main validity issues encountered were as follows:

—Estimates are based on results from studies carried out in populations that are at greater risk of infection or at greater risk of developing complications than the population for which the programme is designed.
—Several risk assumptions are made solely based on case-control data. Although they are very useful, it is impossible to derive absolute risks of complications from these studies.
—At the time of diagnosis of the complication, the occurrence of the tubal factor infertility or ectopic pregnancy is attributed to a sub-clinical chlamydial PID, in the absence of any other apparent cause (diagnosis by exclusion).
—It has also become apparent that there are still great gaps in current knowledge about the natural course of a chlamydial infection; gaps that are, at present, filled by unsubstantiated assumptions.
—Misclassification and incorrect diagnoses. For example, chlamydia might be considered the cause of the complication, whilst at the same time it is retrospectively used as an instrument to diagnose the complication. The clear starting point of scientists in this field of research is the concept that *C. trachomatis* is a serious infection. In some cases, it seems as if the severity of a *C. trachomatis* infection is considered to be almost equal to that of a PID.
—Several mistakes were made in the calculations of the complication rates.

Alternative complication rates

Probabilities calculated on the basis of modelled estimates were systematically higher than the probabilities calculated on the basis of actual data from population registers. The registration data show that probabilities of clinical PID, ectopic pregnancy, and tubal factor infertility are much lower than would have been expected on the basis of current assumptions concerning the probability of complications after chlamydial infection (Table 2). Moreover, the comparison of reported and calculated incidences of ectopic pregnancy and PID in Finland and the US also support the theory that overestimation of current rates is likely.

For the calculation of the observed rates in Amsterdam, data from various sources were used. Data on the incidences of PID and tubal factor infertility were obtained from the Dutch Sentinel Registration.[15,16] The accuracy of these data have been evaluated by Coutinho *et al*. in 1988.[59] The quality of the data is high, although some diagnoses might have been missed and some false-positive diagnoses might have been made.

Furthermore, several assumptions had to be made in the calculations, which may have resulted in errors. In particular, the assumption that the national rate of ectopic pregnancy is similar to the local rate of ectopic pregnancy may be incorrect, as it is known that the incidence of PID is generally higher in urbanized areas than in the rest of the country.[15] Furthermore, data on the seroprevalence of *C. trachomatis* from studies performed in other regions or countries had to be used, as local data on the seroprevalence of *C. trachomatis* in the general population and among women with complications was not always available.

However, the difference between the calculated and the modelled estimates is such that, even if the local seroprevalence is different and the incidence of complications higher, it seems fair to assume that current assumptions regarding the risk of *C. trachomatis* infections overestimate the probability of complications.

Sub-clinical PID and chronic pelvic pain were not included in the calculations for the probability of complications due to *C. trachomatis* infections, mainly because chronic pelvic pain and sub-clinical PID, by definition, are not well documented. The concept of sub-clinical PID remains difficult to grasp. All the available evidence is retrospective and diagnosis is 'by exclusion'. Therefore, it is very difficult to determine causality and to quantify the risk. It may be a very helpful concept to promote the understanding of the pathogenesis of complications with an otherwise undefined cause, but at the same time it is a poorly defined and inadequately quantifiable entity for the purpose of clinical epidemiological studies.

Consequences of the findings

The cost-effectiveness of a screening programme is highly sensitive to the estimate used for PID.[10,60] In populations with a low prevalence of *C. trachomatis*, such as general practice populations or the general population in areas with a low circulation of infection, the predicted cost savings based on current assumptions may disappear when using more realistic estimates for complications.

Cost savings per averted outcome in low prevalence areas will decrease, making screening less efficient. The effect is perhaps greatest in populations with a prevalence that lies around or just above the currently assumed break-even prevalence (2–10%). Lower probabilities of complications, particularly PID, imply fewer complications and associated costs that can be prevented by a screening programme. For those areas, or in those populations in which the prevalence is high, e.g. in most STD clinics and gynaecology and obstetrics departments, or even in pre-defined high-risk sub-groups, the benefits of screening will be less than presently assumed, but may still be considerable.

In conclusion, current assumptions with regard to the risk of asymptomatic *C. trachomatis* infections overestimate the probability of complications. The result is an overestimation of the health gain and cost savings associated with a screening programme. The effect on the health policy is potentially the greatest in populations with a low prevalence, since the currently assumed cost savings associated with screening may disappear when using more realistic estimates for complications.

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KEY MESSAGES

- Current assumptions about the incidence of complications overestimate the true complication rate.
- There are large gaps in knowledge about the natural course of asymptomatic *Chlamydia trachomatis* infections, which are, at present, filled by unsubstantiated assumptions.
- The overestimation of complication rates leads to an overestimation of the health gain and cost savings associated with a screening programme.

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